15

1. A compound having the generalized structural formula

$$X - (CR^{4}_{2}) - J (-G^{4})_{q}$$

$$A - B - R^{1}$$

$$D = E - G^{3})_{q}$$

wherein

 R^1 and R^2 :

- i) independently represent H or lower alkyl;
- ii) together form a bridge of structure

wherein binding is achieved via the terminal carbon atoms;

iii) together form a bridge of structure

wherein binding is achieved via the terminal carbon atoms; or

iv) together form a bridge of structure

$$T^1$$
 $T^1 = T^1$

wherein one or two ring members T¹ are N and the others are CH, and binding is achieved via the terminal atoms; and

wherein

m is 0 or an integer 1-4; and

G¹ is a substituent independently selected from the group consisting of

- $-N(R^6)_2$;
- -NR³COR⁶;



alkyl; cycloalkyl; lower alkenyl; lower cycloalkenyl; halogen-substituted alkyl; amino-substituted alkyl; N-Nower alkylamino-substituted alkyl; N,N-di-lower alkylamino-substituted alkyl; N-lower alkanoylamino-substituted alkyl; 10 hydroxy-substituted alkyl; cyano-substituted alkyl; CONUMNIA . COHOLO carboxy-substituted alkyl; lower alkoxycarbonyl-substituted alkyl; 15 phenyl lower alkoxycarbonyl-substituted alkyl; halogen-substituted alkylamino; amino-substituted alkylamino; N-lower alkylamino-substituted alkylamino; N,N-di-lower alkylamino-substituted alkylamino; 20 N-lower alkanoylamino-substituted alkylamino; hydroxy-substituted alkylaming; cyano-substituted alkylamino; carboxy-substituted alkylamino; lower alkoxycarbonyl-substituted alkylamino; 25 phenyl-lower alkoxycarbonyl-substituted alkylamino; $-OR^6$; $-SR^6$; $-S(O)R^6$; $-S(O)_2R^6$; 30 halogenated lower alkoxy;

halogen;

halogenated lower alkylthio;

15

20

25

halogenated lower alkylsulfonyl;

- -OCOR⁶;
- -COR⁶;
 - $-CO_2R^6$;
- - CH_2OR^3 ;
- $-NQ_2$;
- , -CN;
- amiding;
- guaniding
- sulfo;
- -B(OH)2;
- optionally substituted aryl;
- optionally substituted heteroaryl;
- optionally substituted saturated heterocyclyl;
- optionally substituted partially unsaturated heterocyclyl;
- $-OCO_2R^3$;
- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- -S(O)_p(optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- -S(O)_p(optionally substituted heteroarylalkyl);
- -CHO;
- $-OCON(R^6)_2$;
- $-NR^3CO_2R^6$;
- $-NR^3CON(R^6)_2$

R³ is H or lower alkyl;

30 R⁶ is independently selected from the group consisting of

- H;
- alkyl;

- optionally substituted aryl;
- optionally substituted aryl lower alkyl; and

R⁴ is H, halogen, or lower alkyl;

5

15

20

p is 0, 1, or 2;

X is selected from the group consisting of O, S, and NH;

ÁI

10 Y is selected from the group consisting of

- $-(CR^4_2)_n$ - $S(Q)_p$ -(5-membered heteroaryl)- $(CR^4_2)_s$ -;
- $-(CR_2)_n-C(G(R^4)-(CR_2)_s-;$

wherein

n and s are each independently 0 or an integer of 1-2; and

 G^2 is selected from the group consisting of -CN, -CO₂R³, -CON(R⁶)₂, and -CH₂N(R⁶)₂;

- -O-CH₂-;
- -S(O)-;
- $-S(O)_2-$;
- -SCH₂-;
 - -S(O)CH₂-;
 - -S(O)₂CH₂-;
 - -CH₂S(O)-; and
 - -CH₂S(O)₂-

25

A and D independently represent N or CH;

B and E independently represent N or CH;

L represents N or CH;

with the provisos that

- 30
- a) the total number of N atoms in the ring containing A, B, D, E, and L is 1, 2, or 3; and
- b) when L represents CH, at least one of A and D is an N atom;

q is 0, 1, or 2;

G³ is selected from the group consisting of

- ower alkyl;
- 5 $-NR^3COR^6$;
 - carboxy-substituted alkyl;
 - lower alkoxycarbonyl-substituted alkyl;
 - -OR⁶;
 - -SR⁶;
- 10 -S(O)R⁶;
 - $-S(O)_2R^6$;
 - -OCOR⁶;
 - -COR⁶;
 - -CO₂R⁶;
- -CH₂OR³;
 - $-CON(R^6)_2$;
 - $-S(O)_2N(R^6)_2$;
 - -NO₂;
 - -CN;
- optionally substituted aryl;
 - optionally substituted heteroaryl;
 - optionally substituted saturated heterocyclyl;
 - optionally substituted partially unsaturated heterocyclyl;
 - optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
 - -S(O)_p(optionally substituted heteroaryl);
 - optionally substituted heteroarylalkylaxy;
 - -S(O)₀(optionally substituted heteroary alkyl);
 - $-OCON(R^6)_2$;
- 30 $-NR^3CO_2R^6$;
 - $-NR^3CON(R^6)_2$;

J is a ring selected from the group consisting of

- aryl;
- pyridyl; and
- cycloalkyl;

15

5

q' represents the number of substituents G⁴ on ring J and is 0, 1, 2, 3, 4, or 5, and G⁴ moieties are selected from the group consisting of

- $-N(R^6)_{2}$;
- $-NR^3COR^6$;
- 10 halogen;
 - alkyl;
 - cycloalkyl;
 - lower alkenyl;
 - lower cycloalkenyl;
 - - halogen-substituted alkyl;
 - amino-substituted alkyl;
 - N-lower alkylamino-substituted alkyl;
 - N,N-di-lower alkylamino substituted alkyl;
 - N-lower alkanoylamino-substituted alkyl;
- 20 hydroxy-substituted alkyl;
 - cyano-substituted alkyl;
 - carboxy-substituted alkyl;
 - lower alkoxycarbonyl-substituted alkyl;
 - phenyl lower alkoxycarbonyl-substituted alkyl;
- 25 halogen-substituted alkylamino;
 - amino-substituted alkylamino;
 - N-lower alkylamino-substituted alkylamino;
 - N,N-di-lower alkylamino-substituted alkylamino;
 - N-lower alkanoylamino-substituted alkylamino;
- 30 hydroxy-substituted alkylamino;
 - cyano-substituted alkylamino;
 - carboxy-substituted alkylamino;

- lower alkoxycarbonyl-substituted alkylamino;
- phenyl-lower alkoxycarbonyl-substituted alkylamino;
- - QR6
- -SR
- -S(O)R
 - -S(O)₂R
 - halogenated lower alkoxy;
 - halogenated lower alkylthio;
 - halogenated lower alkylsulfonyl;
- 10 -OCOR⁶;
 - $-COR^6$;
 - $-CO_2R^6$;
 - $-CON(R^6)_2$;
 - $-CH_2OR^3$;
- 15 -NO₂;
 - -CN;
 - amidino;
 - guanidino;
 - sulfo;
- -B(OH)2;
 - optionally substituted aryl;
 - optionally substituted heteroaryl;
 - · optionally substituted saturated heterocyclyl;
 - optionally substituted partially unsaturated heterocyclyl;
- \bullet -OCO₂R³;
 - optionally substituted heteroarylalkyl;
 - optionally substituted heteroaryloxy;
 - -S(O)_p(optionally substituted heteroaryl);
 - optionally substituted heteroarylalkyloxy;
- -S(O)_p(optionally substituted heteroarylalkyl);
 - -CHO;

-OCON(\mathbb{R}^6)₂;

- $-NR^3CO_2R^6$;
- -NR3CON(R6)2
- fused ring-forming bridges attached to and connecting adjacent positions of ring I, said bridges having the structures:

a)

T²

wherein

each T² independently represents N, CH, or CG⁴; T³ represents S, O, CR⁴G⁴, C(R⁴)₂, or NR³; and binding to ring Ais achieved via terminal atoms T² and T³;

b)



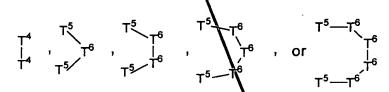
wherein

each T² independently represents N, CH, or CG⁴;

with the proviso that a maximum of two bridge atoms T² may be N; and

binding to ring J is achieved via terminal atoms T2; and

· c)_.



wherein

each T⁴, T⁵, and T⁶ independently represents O, S, CR⁴G⁴, C(R⁴)₂, or NR³; and

binding to ring J is achieved via terminal atoms T^4 or T^5 ; with the provisos that:

- i) when one T^4 is O, S, or NR³, the other T^4 is CR^4G^4 or $C(R^4)_2$;
- ii) a bridge comprising T⁵ and T⁶ atoms may contain a maximum of two heteroatoms O, S, or N; and

طر ک A'

10

5

15

20

- iii) in a bridge comprising T⁵ and T⁶ atoms, when one T⁵ group and one T⁶ group are O atoms, or two T⁶ groups are O atoms, said O atoms are separated by at least one carbon atom;
- and with the further provisos that: 5
 - in G^1 , G^3 , and G^4 , when two groups R^6 are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or NR³ to form a N-containing heterocycle of 5-7 ring atoms; and
 - when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 5\substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkylsubstituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio, lower alkanoyloxy, -CO₂R³, -CHO, -CH₂OR³, -OCO₂R³, -CON(R⁶)₂, -OOO N(R⁶)₂, -NR³CON(R⁶)₂, nitro, amidino, guanidino, mercapto, sulfo, and cyano;

or a pharmaceutically acceptable salt of prodrug thereof.

2. A compound having the generalized structural formula 20

$$\begin{array}{c}
 & H \\
 & (CH_2)_p \\
 & R^4 \\
 & R^2 \\
 & D \\
\end{array}$$

$$\begin{array}{c}
 & G^4 \\
 & Q^4 \\$$

wherein

 R^1 and R^2 :

i) together form a bridge of structure

wherein binding is achieved via the terminal carbon atoms; or

15

ii together form a bridge of structure

wherein one of the ring members T¹ is N and the others are CH, and binding is achieved via the terminal atoms; and

wherein

m is 0 or an integer 1-2; and

G¹ is a substituent independently selected from the group consisting of

- $-N(R^6)_2$;
- -NR³COR⁶;
- halogen;
- alkyl;
- amino-substituted alkylamino;
- N-lower alkylamino-substituted alkylamino;
- N,N-di-lower alkylamino substituted alkylamino;
- N-lower alkanoylamino-substituted alkylamino;
- hydroxy-substituted alkylamino;
- carboxy-substituted alkylamino;
- lower alkoxycarbonyl-substituted alkylamino;
- $-OR^6$;
- $-SR^6$;
- $-S(O)R^6$;
- $-S(O)_2R^6$;
- halogenated lower alkoxy;
- halogenated lower alkylthio;
- halogenated lower alkylsulfonyl;
- -OCOR⁶;
- -COR⁶;
- -CO₂R⁶;

10

15

20

25

- $-CON(R^6)_2$;
- -NO₂;
- -CN;
- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
 - -S(O)_p(optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- \\$(O)_p(optionally substituted heteroarylalkyl);
- 10 R³ is H or lower alkyl;

R⁶ is independently selected from the group consisting of

- H;
- lower alkyl;
- optionally substituted aryl;
 - optionally substituted aryl lower alkyl; and

p is 0 or 1;

- 20 Y is selected from the group consisting of
 - $-(CH_2)_n$ - $S(O)_p$ -(5-membered heteroaryl)- $(CH_2)_s$ -;
 - -(CH₂)_n-C(G²)(H)-(CH₂)_s-; wherein

n and s are each independently 0 or 1; and

 G^2 is selected from the group consisting of -CN, -CO₂R³, -CON(R⁶)₂, and -CH₂N(R⁶)₂;

- -O-CH₂-;
- -S(O)-;
- $-S(O)_{2}$ -;
- **3**0 **•** -SCH₂−;
 - -S(O)CH₂-;
 - $-S(O)_2CH_2-$;

30

-CH₂S(O)-; and -CH₂S(O)₂-

A and Dindependently represent N or CH;

5 L represents N or CH;

with the provisos that

- a) the total number of N atoms in the ring containing A, D, and L is 1 or 2; and
- b) when L represents CH, at least one of A and D is an N atom;

q is 0, 1, or 2; 10

G³ is selected from the group consisting of

- lower alkyl;
- -NR³COR⁶;
- $-OR^6$; 15
 - -SR⁶;
 - $-S(O)R^6$;
 - $-S(O)_2R^6$;
 - $-CO_2R^6$;
 - - $-CON(R^6)_2$;
 - $-S(O)_2N(R^6)_2$;
 - -CN;
 - optionally substituted aryl;
 - optionally substituted heteroaryl;
- 25 optionally substituted heteroarylalkyl;
 - optionally substituted heteroaryloxy;
 - -S(O)_p(optionally substituted heteroaryl);
 - optionally substituted heteroarylalkyloxy;
 - -S(O)_n(optionally substituted heteroarylalkyl);

g' represents the number of substituents G⁴ on the phenyl ring and is 0, 1, 2, or 3; and

d⁴ moieties are selected from the group consisting of $-N(R^6)_2$; -NR3COR6; halogen; 5 alkyl; haldgen-substituted alkyl; hydroxy-substituted alkyl; carboxy-substituted alkyl; lower alkoxycarbonyl-substituted alkyl; 10 amino-substituted alkylamino; N-lower alkylamino-substituted alkylamino; N,N-di-lower alkylamino-substituted alkylamino; COMUNICATORIO N-lower alkanovlamino-substituted alkylamino; hydroxy-substituted alkylamino; carboxy-substituted alkylamino; 15 lower alkoxycarbonyl-substituted alkylamino; phenyl-lower alkoxycarbonyl-substituted alkylamino; $-OR^6$; -SR⁶; $-S(O)R^6$; 20 $-S(O)_2R^6$; halogenated lower alkoxy; halogenated lower alkylthio; halogenated lower alkylsulfonyl; -OCOR6; 25 -COR⁶; $-CO_2R^6$; $-CON(R^6)_2$; -CH₂OR³;

-NO₂;

-CN;

10

15

20

- optionally substituted heteroarylalkyl;
- •\ optionally substituted heteroaryloxy;
- \(\sigma(O)_p(\text{optionally substituted heteroaryl});\)
- optionally substituted heteroarylalkyloxy;
- -S(O) (optionally substituted heteroarylalkyl);
- fused ring-forming bridges attached to and connecting adjacent positions of the phenyl ring, said bridges having the structures:

a)

T₁²/₁

wherein

each T² independently represents N, CH, or CG⁴;

T³ represents S, Q, CHG⁴, CH₂, or NR³; and

binding to the phenyl ring is achieved via terminal atoms T^2 and T^3 ;

b)

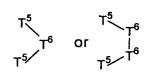
wherein

each T² independently represents N, CH, or CG⁴;

with the proviso that a maximum of two bridge atoms T^2 may be N; and

binding to the phenyl ring is achieved via terminal atoms T²; and

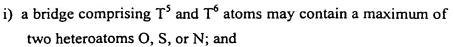
c)



wherein

each T⁵, and T⁶ independently represents O₁ S, CHG⁴, CH₂, or NR³; and

binding to the phenyl ring is achieved via terminal atoms T⁵; with the provisos that:



ii) in a bridge comprising T⁵ and T⁶ atoms, when one T⁵ group and one T⁶ group are O atoms, or two T⁶ groups are O atoms, said O atoms are separated by at least one carbon atom;

5

SUBAL

and with the further provisos that:

- in G^1 , G^2 , G^3 , and G^4 , when two groups R^6 are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or NR^3 to form a N-containing heterocycle of 5-7 ring atoms; and
- when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 2 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio, lower alkanoyloxy, -CO₂R³, -CH₂OR³, -OCO₂R³, -CON(R⁶)₂, -OCO N(R⁶)₂, -NR³CON(R⁶)₂, nitro, and cyano;

or a pharmaceutically acceptable salt or prodrug thereof.

20

15

3. A compound having the generalized structural formula

wherein

 R^1 and R^2 :

25

i) together form a bridge of structure

$$=$$
 $G^1)_m$

wherein binding is achieved via the terminal carbon atoms, and any group G¹ is located on a non-terminal atom of the bridge; or

10

15

25

30

N) together form a bridge of structure

wherein one of the ring members T¹ is N and the others are CH, and binding is achieved via the terminal atoms; and

wherein

m is 0 or an integer 1-2; and

G¹ is a substituent independently selected from the group consisting of

- $-N(R^6)_2$;
- -NR³COR⁶;
- halogen;
- -OR⁶ wherein Rorepresents lower alkyl;
- -NO₂;
- optionally substituted heteroaryloxy;
- optionally substituted heteroarylalkyloxy;

R³ is H or lower alkyl;

20 R⁶ is independently selected from the group consisting of

- H;
- lower alkyl;
- optionally substituted aryl;
- optionally substituted aryl lower alkyl; and

p is 0 or 1;

Y is selected from the group consisting of

- -S(O)_p-(5-membered heteroaryl)-;
- -C(CN)(H)-;
- -O-CH₂-;

-S(O)-; and -S(O)₂-; q 1 0 or 1; 5 G³ is selected from the group consisting of lower alkyl; -NRCOR6; -CO₂R -CON(R **1**2; 10 $-S(O)_2N(R^3)_2$; q' represents the number of substituents G⁴ on the phenyl ring and is 0, 1, 2, or 3; G⁴ moieties are selected from the group consisting of 15 $-N(R^6)_2$; halogen; lower alkyl; halogen-substituted lower alkyl $-OR^6$; 20 -SR⁶; $-S(O)R^6$; $-S(O)_2R^6$; halogenated lower alkoxy; 25 halogenated lower alkylthio; halogenated lower alkylsulfonyl; -OCOR⁶; -COR⁶; $-CO_2R^6$; -CON $(R^6)_2$; 30 -CH₂OR³; $-NO_2$;

-CN;

- \optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- -S(O)p(optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- -S(O)_p(optionally substituted heteroarylalkyl);
- fused ring-forming bridges attached to and connecting adjacent positions of the phenyl ring, said bridges having the structures:

a)

T₁²
T

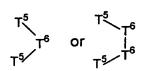
wherein

each T² independently represents N, CH, or CG⁴;

T³ represents S, O, CHG⁴, CH₂, or NR³; and

binding to the phenyl ring is achieved via terminal atoms T² and T³;

b)



wherein

each T⁵, and T⁶ independently represents O, S, CHG⁴, CH₂, or NR³; and

binding to the phenyl ring is achieved via terminal atoms T⁵; with the provisos that:

- i) a bridge comprising T⁵ and T⁶ atoms may contain a maximum of two heteroatoms O, S, or N; and
- ii) in a bridge comprising T⁵ and T⁶ atoms, when one T⁵ group and one T⁶ group are O atoms, or two T⁶ groups are O atoms, said O atoms are separated by at least one carbon atom;

5 Jb A 1

10

15

20

and with the further provisos that:

- in G^1 , G^3 , and G^4 , when two groups R^6 are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or NR³ to form a N-containing heterocycle of 5 6 ring atoms; and
- when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 2 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio, -CO₂R³, -CON(R⁶)₂, nitro, and cyano;

or a pharmaceutically acceptable salt or prodrug thereof.

10

A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

20

- 5. A method of treating a mammal having a condition characterized by abnormal angiogenesis or hyperpermiability processes, comprising administering to said mammal an amount of a compound of claim 1 which is effective to treat said condition.
- 6. The method of claim 5, wherein said condition is tumor growth; retinopathy, including diabetic retinopathy, ischemic rechal-vein occlusion, retinopathy of prematurity, and age-related macular degeneration; rheumatoid arthritis; psoriasis; or a bullous disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, and dermatitis herpet formis.
- 7. A compound having the generalized structural formula



$$X-(CR^{4}_{2}) \longrightarrow J \longrightarrow G^{4}_{q}$$

$$A-B \longrightarrow R^{2}$$

$$D=E \longrightarrow G^{3}_{q}$$

wherein

R¹ and R²:

- i) independently represent H or lower alkyl;
- ii) together form a bridge of structure

$$\left\langle \begin{array}{c} C \\ C \end{array} \right\rangle_{n}$$

wherein binding is achieved via the terminal carbon atoms;

iii) together form a bridge of structure

wherein binding is achieved via the terminal carbon atoms; or

iv) together form a bridge of structure

$$T^1$$
 $T^1 = T^1$

wherein one or two ring members T¹ are N and the others are CH, and binding is achieved via the terminal atoms; and

wherein

m is 0 or an integer 1-4; and

G¹ is a substituent independently selected from the group consisting of

- $-N(R^6)_2$;
 - -NR³COR⁶;
 - halogen;
 - alkyl;
 - cycloalkyl;
 - lower alkenyl;
 - lower cycloalkenyl;
 - halogen-substituted alkyl;
 - amino-substituted alkyl;
 - N-lower alkylamino-substituted alkyl;
 - N,N-di-lower alkylamino-substituted alkyl;



5

10

20

15

			 N-lower alkanoylamino-substituted alkyl;
			 hydroxy-substituted alkyl;
		\	cyano-substituted alkyl;
		\	carboxy-substituted alkyl;
_ 1	5		• lower alkoxycarbonyl-substituted alkyl;
5 Jy	<i>'</i>		 phenyl lower alkoxycarbonyl-substituted alkyl;
A	3		halogen-substituted alkylamino;
• •			ammo-substituted alkylamino;
			N-lower alkylamino-substituted alkylamino;
	10		N,N-di-lower alkylamino-substituted alkylamino;
			N-lower alkanoylamino-substituted alkylamino;
			hydroxy-substituted alkylamino;
			cyano-substituted alkylamino;
u M			carboxy-substituted alkylamino;
Ŋ	15		• lower alkoxycarbonyl-substituted alkylamino;
Ū			• phenyl-lower alkoxycarbonyl-substituted alkylamino;
Ō			• -OR ⁶ ;
Ø ⊭			• -SR ⁶ ;
			• $-S(O)R^6$;
	20		• $-S(O)_2R^6$;
			halogenated lower alkoxy;
			halogenated lower alkylthio;
			halogenated lower alkylsulfonyl;
			• -OCOR ⁶ ;
	25		• -COR ⁶ ;
			• $-CO_2R^6$;
			• $-CON(R^6)_2$;
			• -CH ₂ OR ³ ;
			• -NO ₂ ;
	30		• -CN;
		•	amidino;

		• sulfo;
		• -B(OH)2;
		 optionally substituted aryl;
	5	 optionally substituted heteroaryl;
	6	optionally substituted saturated heterocyclyl;
5	עיע	 optionally substituted partially unsaturated heterocyclyl;
	dy A3	• -OCO ₂ R ³ ;
	•	 optionally substituted heteroarylalkyl;
	10	 optionally substituted heteroaryloxy;
		 -S(O)_p(optionally substituted heteroaryl);
		 optionally substituted heteroarylalkyloxy;
oomuss, ootoo		 -S(O)_p(optionally substituted heteroarylalkyl);
u Li		• -CHO;
u: U	15	• -OCON(R ⁶) ₂ ;
i i		• $-NR^3CO_2R^6$;
5 ===		• $-NR^3CON(R^6)_2$
w W		
j S		R ³ is H or lower alkyl;
	20	
hal		R ⁶ is independently selected from the group consisting of
		• H;
		alkyl;
		optionally substituted aryl;
	25	 optionally substituted aryl lower alkyl; and
		\
		R ⁴ is H, halogen, or lower alkyl;
		\

guanidino;

30

p is 0, 1, or 2;

X is selected from the group consisting of O, S, and NH,

Y is selected from the group consisting of lower alkylene, optionally substituted by OH or OAcyl; -CH₂-O-; CH_2-S- ; **Ċ**₩2-NH-; 5 -0- ; -S-; -NH-; $-(CR_2^4)_n$ - $S(O)_p$ -(5-membered heteroaryl)- $(CR_2^4)_s$ -; $-(CR_{2}^{4})_{n}-C(G^{2})(R^{4})-(CR_{2}^{4})_{s}$; 10 wherein n and s are each independently 0 or an integer of 1-2; and G² is selected from the group consisting of -CN, -CO₂R³, -CON(R⁶)₂, and $-\dot{C}H_2N(R^6)_2$; 15 -O-CH₂-; -S(O)-; $-S(O)_2-;$ -SCH₂-; $-S(O)CH_2-;$ $-S(O)_2CH_2-$; 20 -CH2S(O)-; and -CH₂S(O)₂-A and D independently represent N or CH; 25 B and E independently represent N or CH; L represents N or CH; with the provisos that a) the total number of N atoms in the ring containing A, B, D, E, and L is 1, 2, or

30

b) when L represents CH, at least one of A and D is an N atom;

q is 0, 1, or 2;

3; and

25

G is selected from the group consisting of -NR³COR⁶;

- carboxy-substituted alkyl;
- lower alkoxycarbonyl-substituted alkyl;
- -OR\(\frac{1}{2}\):
- -SR⁶;
- $-S(O)R^6$;
- $-S(O)_2R^6$;
- -OCOR⁶;
- 10 -COR⁶;
 - $-CO_2R^6$;
 - $-CH_2OR^3$;
 - $-CON(R^6)_2$;
 - $-S(O)_2N(R^6)_2$;
- 15 -NO₂;
 - -CN;
 - optionally substituted aryl;
 - optionally substituted heteroaryl;
 - optionally substituted saturated heterocyclyl;

optionally substituted partially unsaturated heterocyclyl;

- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- -S(O)_p(optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- -S(O)_p(optionally substituted heteroarylalkyl);
 - $-OCON(R^6)_2$;
 - -NR³CO₂R⁶;
 - $-NR^3CON(R^6)_2$;
- J is a ring selected from the group consisting of
 - aryl;

15

- pyridyl; and
- cycloalkyl;
- q' represents the number of substituents G^4 on ring J and is 0, 1, 2, 3, 4, or 5, and G^4 moieties are selected from the group consisting of
 - $-N(R^6)_2$;
 - $-NR^3COR^6$;
 - halogen
 - alkyl;
- 10 cycloalkyl;
 - lower alkenyl;
 - lower cycloalkenyl
 - halogen-substituted alkyl;
 - amino-substituted alkyly
 - N-lower alkylamino-substituted alkyl;
 - N,N-di-lower alkylamino-substituted alkyl;
 - N-lower alkanoylamino-substituted alkyl;
 - hydroxy-substituted alkyl;
 - cyano-substituted alkyl;
 - carboxy-substituted alkyl;
 - lower alkoxycarbonyl-substituted alkyl;
 - phenyl lower alkoxycarbonyl-substituted alkyl;
 - halogen-substituted alkylamino;
 - amino-substituted alkylamino;
- N-lower alkylamino-substituted alkylamino;
 - N,N-di-lower alkylamino-substituted alkylamino;
 - N-lower alkanoylamino-substituted alkylamino,
 - hydroxy-substituted alkylamino;
 - cyano-substituted alkylamino;
- carboxy-substituted alkylamino;
 - lower alkoxycarbonyl-substituted alkylamino;

phenyl-lower alkoxycarbonyl-substituted alkylamino; -OR⁶; §R⁶: $-S(O)_{\mathbb{R}}R^{6};$ 5 halogenated lower alkoxy; halogenated lower alkylthio; halogenated lower alkylsulfonyl; -OCOR⁶; -COR⁶; 10 $-CO_2R^6$; $-CON(R^6)_2$; 0 0 0 -CH₂OR³; L D $-NO_2$; -CN; 15 amidino; guanidino; sulfo; -B(OH)2; 20 optionally substituted aryl; optionally substituted heteroaryl; optionally substituted saturated heterocyclyl; optionally substituted partially unsaturated heterocyclyl; $-OCO_2R^3$; optionally substituted heteroarylalkyl; 25 optionally substituted heteroaryloxy; -S(O)_p(optionally substituted heteroaryl); optionally substituted heteroarylalkyloxy; -S(O)_p(optionally substituted heteroarylalkyl); 30 -CHO; $-OCON(R^6)_2$;

10

15

-NR 3 CO $_2$ R 6 ;

- $NR^3CON(R^6)_2$
- fused ring-forming bridges attached to and connecting adjacent positions of ring J, said bridges having the structures:

a)

L₃

wherein

each T² independently represents N, CH, or CG⁴; T³ represents S, O, CR⁴G⁴, C(R⁴)₂, or NR³; and binding to ring I is achieved via terminal atoms T² and T³;

b)



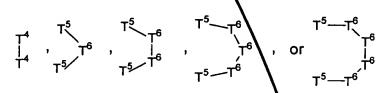
wherein

each T² independently represents N, CH, or CG⁴;

with the proviso that a maximum of two bridge atoms T² may be N;

binding to ring J is achieved via terminal atoms T2; and

c)



20

wherein

each T⁴, T⁵, and T⁶ independently represents O, S, CR⁴G⁴, C(R⁴)₂, or NR³; and

binding to ring J is achieved via terminal atoms T^4 or T^5 ; with the provisos that:

- i) when one T^4 is O, S, or NR³, the other T^4 is CR^4G^4 or $C(R^4)_2$;
- ii) a bridge comprising T⁵ and T⁶ atoms may contain a maximum of two heteroatoms O, S, or N; and

- iii) in a bridge comprising T⁵ and T⁶ atoms, when one T⁵ group and one T⁶ group are O atoms, or two T⁶ groups are O atoms, said O atoms are separated by at least one carbon atom;
- 5 and with the further provisos that:
 - in G¹, G², G³, and G⁴, when two groups R⁶ are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or NR³ to form a N-containing heterocycle of 5 7 ring atoms; and
 - when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 5 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio, lower alkanoyloxy, -CO₂R³, -CHO, -CH₂OR³, -OCO₂R³, -CON(R⁶)₂, -OCO N(R⁶)₂, -NR³CON(R⁶)₂, nitro, amidino, guanidino, mercapto, sulfo, and cyano;

or a pharmaceutically acceptable salt or prodrug thereof.

20 8. A compound having the generalized structural formula

wherein

 R^1 and R^2 :

i) together form a bridge of structure



wherein binding is achieved via the terminal carbon atoms; or

15

20

25

(ii) together form a bridge of structure

$$T^1$$
 $T^1 = T^1$

wherein one of the ring members T¹ is N and the others are CH, and binding is achieved via the terminal atoms; and

wherein

m is 0 or an integer 1-2; and

G¹ is a substituent independently selected from the group consisting of

- $-N(R^6)_2$;
- -NR³COR⁶;
- halogen;
- alkyl;
- amino-substituted alkylamino;
- N-lower alkylamino-substituted alkylamino;
- N,N-di-lower alkylamino-substituted alkylamino;
- N-lower alkanoylamino-substituted alkylamino;
- hydroxy-substituted alkylamino;
- carboxy-substituted alkylamino;
- lower alkoxycarbonyl-substituted alkylamino;
- $-OR^6$;
- $-SR^6$;
- $-S(O)R^6$;
- $-S(O)_2R^6$;
- halogenated lower alkoxy;
 - halogenated lower alkylthio;
 - halogenated lower alkylsulfonyl;
 - -OCOR⁶;
 - -COR⁶;
- 0 -CO₂R⁶;

 $-CON(R^6)_2$; -NO₂; -CN; optionally substituted heteroarylalkyl; 5 optionally substituted heteroaryloxy; -S(O)_p(optionally substituted heteroaryl); optionally substituted heteroarylalkyloxy; -S(Q)p(optionally substituted heteroarylalkyl); R³ is H or lower alkyl; 10 R⁶ is independently selected from the group consisting of H; lower alkyl; 15 optionally substituted aryl; optionally substituted aryl lower alkyl; and p is 0 or 1; Y is selected from the group consisting of 20 lower alkylene, optionally substituted by OH or OAcyl; -CH₂-O-; -CH₂-S-; -CH₂-NH-; 25 -O-; -S-; -NH-; - $(CH_2)_n$ - $S(O)_p$ -(5-membered heteroaryl)- $(CH_2)_s$ -;

30 wherein

n and s are each independently 0 or 1; and

 $-(CH_2)_n-C(G^2)(H)-(CH_2)_s-$;

```
G^2 is selected from the group consisting of -CN, -CO<sub>2</sub>R<sup>3</sup>, -CON(R<sup>6</sup>)<sub>2</sub>, and
                                 -CH_2N(R^6)_2;
                        -O-CH<sub>2</sub>-;
                         S(O)-;
   5
                       -S(O) (H<sub>2</sub>-
                       -S(O)<sub>2</sub>CN<sub>2</sub>-
                       -CH_2S(O)-\backslash and
  10
                       -CH<sub>2</sub>S(O)<sub>2</sub>-
             A and D independently represent N or CH;
             L represents N or CH;
                  with the provisos that
                  a) the total number of N atoms in the ring containing A, D, and L is 1 or 2; and
 15
                 b) when L represents CH, at least one of A and D is an N atom;
             q is 0, 1, or 2;
             G<sup>3</sup> is selected from the group consisting of
20
                     -NR3COR6;
                 •- -OR^6;
                     -SR<sup>6</sup>;
                    -S(O)R^6;
                    -S(O)_2R^6;
25
                   -CO<sub>2</sub>R<sup>6</sup>;
                    -CON(R^6)_2;
                    -S(O)_2N(R^6)_2;
                     -CN;
30
                    optionally substituted aryl;
                    optionally substituted heteroaryl;
                    optionally substituted heteroarylalkyl;
```

- optionally substituted heteroaryloxy;
- -S(O)_p(optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
 - -S(O)_p(optionally substituted heteroarylalkyl);

Sub

- q' represents the number of substituents G⁴ on the phenyl ring and is 0, 1, 2, or 3; and
- G⁴ moieties are selected from the group consisting of
 - $-N(R^6)_2$
- 10 -NR³COR
 - halogen;
 - alkyl;
 - halogen-substituted alkyl;
 - hydroxy-substituted alkyl;

15

- carboxy-substituted alkyl;
- lower alkoxycarbonyl-substituted alkyl;
- amino-substituted alkylamino;
- N-lower alkylamino-substituted alkylamino;
- N,N-di-lower alkylamino-substituted alkylamino;
- N-lower alkanoylamino-substituted alkylamino;
 - hydroxy-substituted alkylamino;
- carboxy-substituted alkylamino;
- lower alkoxycarbonyl-substituted alkylamino;
- phenyl-lower alkoxycarbonyl-substituted alkylamino;

25

20

- -OR⁶:
- -SR⁶;
- $-S(O)R^6$;
- $-S(O)_2R^6$;
- halogenated lower alkoxy;

30

- halogenated lower alkylthio;
- halogenated lower alkylsulfonyl;
- -OCOR⁶;

10

20

25

```
-COR6;
```

 $-CO_2R^6$;

 $-CON(R^6)_2$;

-CH₂OR³;

- -NO₂;
- CN:

a)

- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- -S(O), (optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- -S(O)₀(optionally substituted heteroarylalkyl);
- fused ring-forming bridges attached to and connecting adjacent positions of the phenyl ring said bridges having the structures:

wherein

each T² independently represents N, CH, or CG⁴;

T³ represents S, O, CHG⁴, C(H)₂, or NR³; and

binding to the phenyl ring is achieved via terminal atoms T² and T³;

b)

wherein

each T² independently represents N, CH, or CG⁴:

with the proviso that a maximum of two bridge atoms T² may be N;

and

binding to the phenyl ring is achieved via terminal atoms T²; and

c)

15

20

25

ioe zesto . cetoo

wherein

each T⁵, and T⁶ independently represents O, S, CHG⁴, C(H)₂, or NR³; and

binding to the phenyl ring is achieved via terminal atoms T^5 ; with the provisos that:

- i) a bridge comprising T⁵ and T⁶ atoms may contain a maximum of two heteroatoms O, S, or N; and
- ii) in a bridge comprising T⁵ and T⁶ atoms, when one T⁵ group and one T⁶ group are O atoms, or two T⁶ groups are O atoms, said O atoms are separated by at least one carbon atom;

and with the further provisos that:

- in G¹, G², G³, and G¹ when two groups R⁶ are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or NR³ to form a N-containing heterocycle of 5 7 ring atoms; and
- when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 2 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio, lower alkanoyloxy, $-CO_2R^3$, $-CH_2OR^3$, $-OCO_2R^3$, $-CON(R^6)_2$, $-OCO_2R^3$, $-OCO_2R^3$

9. A compound having the generalized structural formula

or a pharmaceutically acceptable salt or prodrug thereof.

wherein

10

15

20

 \mathbb{R}^1 and \mathbb{R}^2 :

i) together form a bridge of structure

$$=$$
 $G^1)_m$

wherein binding is achieved via the terminal carbon atoms, and any group G¹ is located on a non-terminal atom of the bridge; or

ii) together form a bridge of structure

wherein one of the ring members T¹ is N and the others are CH, and binding is achieved via the terminal atoms; and

wherein

m is 0 or an integer 1-2; and

G¹ is a substituent independently selected from the group consisting of

- $-N(R^6)_2$;
- $-NR^3COR^6$;
- halogen;
- -OR⁶ wherein R6 represents lower alkyl;
- -NO₂;
- optionally substituted heteroaryloxy;
- optionally substituted heteroarylalkyloxy;

R³ is H or lower alkyl;

25 R⁶ is independently selected from the group consisting of

- H;
- lower alkyl;
- optionally substituted aryl;
- optionally substituted aryl lower alkyl; and

10

15

20

p is 0 or 1;

Y is selected from the group consisting of

- \lower alkylene, optionally substituted by OH;
- \CH₂-O-;
 - -s
 - /"/
 - -S(O) (5-membered heteroaryl)-;
 - -C(CN)(H)-;
 - -O-CH₂-
 - -S(O)-; and
 - -S(O)₂-;

q is 0 or 1;

G³ is selected from the group consisting of

- -NR³COR⁶;
- -CO₂R⁶;
- $-CON(R^6)_2$;
- $-S(O)_2N(R^6)_2$;

q' represents the number of substituents G⁴ on the phenyl ring and is 0, 1, 2, or 3; and

G⁴ moieties are selected from the group consisting of

- 25 $-N(R^6)_2$;
 - halogen;
 - lower alkyl;
 - halogen-substituted lower alkyl;
 - -OR⁶;
- 30 $-SR^6$;
 - $-S(O)R^6$;
 - $-S(O)_2R^6$;

halogenated lower alkoxy;

- halogenated lower alkylthio;
- halogenated lower alkylsulfonyl;
- -dCOR6;
- -COR⁶
- $-CO_2R^6$
- $-CON(R^6)_2$;
- -CH₂OR
- -NO₂;
- 10

15

5

- -CN;
- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- -S(O)_p(optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- -S(O)_p(optionally substituted heteroarylalkyl);
- fused ring-forming bridges attached to and connecting adjacent positions of the phenyl ring, said bridges having the structures:

a)

T² T

20

wherein

each T² independently represents N, CH, or CG⁴;

T³ represents S, O, CHO⁴, CH₂, or NR³; and

binding to the phenyl ring is achieved via terminal atoms T² and T³;

b)

$$T^{5}$$
 T^{6} or T^{5} T^{6}

25

wherein

each T⁵, and T⁶ independently represents O, S, CHG⁴, CH₂, or NR³; and

binding to the phenyl ring is achieved via terminal atoms T^5 ;

with the provisos that:

- i) a bridge comprising T⁵ and T⁶ atoms may contain a maximum of two heteroatoms O, S, or N; and
- ii) in a bridge comprising T⁵ and T⁶ atoms, when one T⁵ group and one T⁶ group are O atoms, or two T⁶ groups are O atoms, said O atoms are separated by at least one carbon atom:

5

10

15

and with the further provisos that:

- in G¹, G², G³, and G⁴, when two groups R⁶ are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or NR³ to form a N-containing heterocycle of 5 - 6 ring atoms; and
- when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 2 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio, $-CO_2R^3$, $-CON(R^6)_2$, nitro, and cyano;

or a pharmaceutically acceptable salt or prodrug thereof.

25

10. A pharmaceutical composition comprising a compound of claim 7 and a pharmaceutically acceptable carried

overselo logicoc

- 11. A method of treating a maminal having a condition characterized by abnormal angiogenesis or hyperpermiability processes, comprising administering to said mammal an amount of a compound of claim 7 which is effective to treat said condition.
- 12. The method of claim 11, wherein said condition is tumor growth; retinopathy, 30 including diabetic retinopathy, isohemic retinal-vein occlusion, retinopathy of prematurity, and age-related macula degeneration; rheumatoid arthritis; psoriasis; or a bullous disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis.

15

13. A compound having the generalized structural formula

wherein

R¹ and R²

- i) independently represent H or lower alkyl;
- ii) together form a bridge of structure



wherein binding is achieved via the terminal carbon atoms;

iii) together form a bridge of structure

$$=$$
 G_1

wherein binding is achieved via the terminal carbon atoms; or

iv) together form a bridge of structure

$$T^1 = T^1$$

wherein one or two ring members T¹ are N and the others are CH, and binding is achieved via the terminal atoms; and

wherein

m is 0 or an integer 1-4; and

20 G¹ is a substituent independently selected from the group consisting of

- $-N(R^6)_2$;
- -NR³COR⁶;
- halogen;
- alkyl;

• cycloalkyl;

lower cycloalkenyl; halogen-substituted alkyl; amino-substituted alkyl; N-lower alkylamino-substituted alkyl; N,N-di-lower alkylamino-substituted alkyl; Nelower alkanoylamino-substituted alkyl; hydroxy-substituted alkyl; cyano substituted alkyl; 10 carboxy-substituted alkyl; lower alkoxycarbonyl-substituted alkyl; phenyl lower alkoxycarbonyl-substituted alkyl; halogen-substituted alkylamino; amino-substituted alkylamino; M N-lower alkylamino-substituted alkylamino; 15 L N,N-di-lower alkylamino-substituted alkylamino; . CELOCI N-lower alkanoylamino-substituted alkylamino; hydroxy-substituted alkylamino; cyano-substituted alkylamino; carboxy-substituted alkylamino; 20 lower alkoxycarbonyl-substituted alkylamino; phenyl-lower alkoxycarbonyl-substituted alkylamino; $-OR^6$; $-SR^6$; $-S(O)R^6$; 25 $-S(O)_2R^6$; halogenated lower alkoxy; halogenated lower alkylthio; halogenated lower alkylsulfonyl; -OCOR⁶; 30 -COR⁶;

lower alkenyl;

 $-CO_2R^6$; $-CON(R^6)_2$; -CH₂OR³; -NO₂; -CN; amidino; guanidino; sulfo; **B**(OH)2; 10 optionally substituted aryl; optionally substituted heteroaryl; optionally substituted saturated heterocyclyl; COCYMULO LOCALOCO optionally substituted partially unsaturated heterocyclyl; $-OCO_2R^3$ optionally substituted heteroarylalkyl; 15 optionally substituted heteroaryloxy; -S(O)_p(optionally substituted heteroaryl); optionally substituted heteroarylalkyloxy; -S(O)p(optionally substituted heteroarylalkyl); 20 -CHO; $-OCON(R^6)_2$; -NR³CO₂R⁶; $-NR^3CON(R^6)_2$ R³ is H or lower alkyl; 25 R⁶ is independently selected from the group consisting of H;

30

optionally substituted aryl;

alkyl;

• optionally substituted aryl lower alkyl; and

p is 0, 1, or 2; 5 X is selected from the group consisting of O, S, and NH; Y is selected from the group consisting of lower alkylene, optionally substituted by OH or OAcyl; -CH₂-O -CH₂-S-; -CH₂-NH-**-**0- ; -S-; -NH-; $-(CR_{2}^{4})_{n}-S(O)_{p}-(5-membered heteroaryl)-(CR_{2}^{4})_{s}-;$ 15 $-(CR_{2}^{4})_{n}-C(G^{2})(R^{4})-(CR_{2}^{4})_{s}-;$ wherein n and s are each independently 0 or an integer of 1-2; and G^2 is selected from the group consisting of -CN, -CO₂R³, -CON(R⁶)₂, and $-CH_2N(R^6)_2$; 20 -O-CH₂-; -S(O)-; $-S(O)_2-;$ -SCH₂-; 25 $-S(O)CH_2-;$ $-S(O)_2CH_2-$; -CH₂S(O)-; and -CH₂S(O)₂-30 A and D independently represent N or CH; B and E independently represent N or CH; L represents N or CH; with the provisos that

20

a) the total number of N atoms in the ring containing A, B, D, E, and L is 1, 2, or 3; and

b) when L represents CH, at least one of A and D is an N atom;

5 q is 0, 1, $\frac{1}{2}$;

5.b 85

G³ is selected from the group consisting of

- lower alkyl;
- -NR³COR⁶;
- carboxy-substituted alkyl;
 - lower alkoxygarbonyl-substituted alkyl;
 - -OR⁶;
 - -SR⁶;
 - $-S(O)R^6$;
 - $-S(O)_2R^6$;
 - -OCOR⁶;
 - -COR⁶;
 - -CO₂R⁶;
 - $-CH_2OR^3$;
 - $-CON(R^6)_2$;
 - $-S(O)_2N(R^6)_2$;
 - -NO₂;
 - -CN;
 - optionally substituted aryl;
- optionally substituted heteroaryl;
 - optionally substituted saturated heterocyclyl;
 - optionally substituted partially unsaturated heterocyclyl;
 - optionally substituted heteroarylalkyl;
 - optionally substituted heteroaryloxy;
- -S(O)_p(optionally substituted heteroaryl);
 - optionally substituted heteroarylalkyloxy;
 - -S(O)_p(optionally substituted heteroarylalkyl);

20

-OCON(R⁶)₂;
 -NR³CO₂R⁶;
 -NR³CON(R⁶)₂;

5 J is a ring selected from the group consisting of

- aryl;
- pyridyl; and
- cycloalkyl

q' represents the number of substituents G⁴ on ring J and is 0, 1, 2, 3, 4, or 5, and G⁴ moieties are selected from the group consisting of

- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- -S(O)_p(optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- -S(O)_p(optionally substituted heteroarylalkyl);
- -CHO;
- $-OCON(R^6)_2$;
- $-NR^3CO_2R^6$;
- $-NR^3CON(R^6)_2$
- fused ring-forming bridges attached to and connecting adjacent positions of ring J, said bridges having the structures:

a)

T² T²

25 wherein

each T² independently represents N, CH, or CG⁴; T³ represents S, O, CR⁴G⁴, C(R⁴)₂, or NR³; and

binding to ring J is achieved via terminal atoms T² and T³;

), b)

wherein

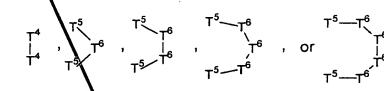
wherein

each T² independently represents N, CH, or CG⁴;

with the proviso that a maximum of two bridge atoms T² may be N; and

binding to ring J is achieved via terminal atoms T²; and

c)



10

15

20

each T⁴, T⁵, and T⁶ independently represents O, S, CR⁴G⁴, C(R⁴)₂, or NR³; and

binding to ring T is achieved via terminal atoms T^4 or T^5 ; with the provisos that:

- i) when one T^4 is O, S, or NR³, the other T^4 is CR^4G^4 or $C(R^4)_2$;
- ii) a bridge comprising T⁵ and T⁶ atoms may contain a maximum of two heteroatoms O, S, or N; and
- iii) in a bridge comprising T^5 and T^6 atoms, when one T^5 is O, the other T^5 is S, CR^4G^4 , $C(R^4)_2$ or NR^3 ;
- iv) in a bridge comprising T⁵ and T⁶ atoms, when one T⁵ group and one T⁶ group are O atoms, or two T⁶ groups are O atoms, said O atoms are separated by at least one carbon atom;

and with the further provisos that:

- in G¹, G², G³, and G⁴, when two groups R⁶ are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or NR³ to form a N-containing heterocycle of 5 – 7 ring atoms; and

10

15

when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 5 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio, lower alkanoyloxy, -CO₂R³, -CHO, -CH₂OR³, -OCO₂R³, -CON(R⁶)₂, -OCO N(R⁶)₂, -NR³CON(R⁶)₂, nitro, amidino, guanidino, mercapto, sulfo, and cyano;

or a pharmaceutically acceptable salt or prodrug thereof.

14. A compound having the generalized structural formula

wherein

 R^1 and R^2 :

i) together form a bridge of structure

wherein binding is achieved via the terminal carbon atoms; or

ii) together form a bridge of structure

$$T^1$$
 $T^1 = T^1$

wherein one of the ring members T¹ is N and the others are CH, and binding is achieved via the terminal atoms; and

wherein

m is 0 or an integer 1-2; and

G¹ is a substituent independently selected from the group consisting of

• $-N(R^6)_2$;

25

		halogen;
		• alkyl;
		amino-substituted alkylamino;
	5	 W-lower alkylamino-substituted alkylamino;
ζ_{ν}	<i>b</i>	 N,V-di-lower alkylamino-substituted alkylamino;
50	AS	 N-lower alkanoylamino-substituted alkylamino;
		 hydroxy-substituted alkylamino;
		 carboxy-substituted alkylamino;
	10	 lower alkoxycarbonyl-substituted alkylamino;
		• -OR ⁶ ;
Ġ		• -SR ⁶ ;
		• -S(O)R ⁶ ;
		• $-S(O)_2R^6$;
Ŋ	15	 halogenated lower alkoxy;
		 halogenated lower alkylthio;
		 halogenated lower alkylsulfonyl;
M H		• -OCOR ⁶ ;
		• -COR ⁶ ;
	20	• -CO ₂ R ⁶ ;
		• $-CON(R^6)_2$;
		• -NO ₂ ;
		• -CN;
		 optionally substituted heteroarylalkyl;
	25	 optionally substituted heteroaryloxy;
		 -S(O)_p(optionally substituted heteroaryl);
		 optionally substituted heteroarylalkyloxy;
		 -S(O)_p(optionally substituted heteroarylalkyl);
	30	R ³ is H or lower alkyl;

• -NR³COR⁶;

 R^6 is independently selected from the group consisting of H;

- lower alkyl;
- aptionally substituted aryl;
- optionally substituted aryl lower alkyl; and

Subj As

5

p is 0 or 1;

Y is selected from the group consisting of

- lower alkylene, optionally substituted by OH or OAcyl;
 - -CH₂-O-;
 - -CH₂-S-;
 - -CH₂-NH-;
 - -O-;
 - -0-
- -S-;
 - -NH-;
 - -(CH₂)_n-S(O)_p-(5-membered heteroaryl)-(CH₂)_s-;
 - $-(CH_2)_n-C(G^2)(H)-(CH_2)_s-$

wherein

20 n and s are each independently 0 or 1; and

 G^2 is selected from the group consisting of -CN, -CO₂R³, -CON(R⁶)₂, and -CH₂N(R⁶)₂;

- -O-CH₂-;
- -S(O)-;
- -S(O)₂-;
 - -SCH₂-;
 - -S(O)CH₂-;
 - -S(O)₂CH₂-;
 - -CH₂S(O)-; and
- -CH₂S(O)₂-

A and D independently represent N or CH;

epresents N or CH; with the provisos that a) the total number of N atoms in the ring containing A, D, and L is 1 or 2; and b) when L represents CH, at least one of A and D is an N atom; 5 q is 0, 1, or 🕻 G³ is selected from the group consisting of lower alkyl; -NR³COR⁶ 10 $-OR^6$; -SR⁶; $-S(O)R^6$; $-S(O)_2R^6$; $-CO_2R^6$; 15 $-CON(R^6)_2$; $-S(O)_2N(R^6)_2$; -CN; optionally substituted aryl; optionally substituted heteroatyl; 20 optionally substituted heteroary alkyl; optionally substituted heteroaryloxy; -S(O)_p(optionally substituted heteroaryl); optionally substituted heteroarylalkyloxy; -S(O)_p(optionally substituted heteroary alkyl); 25 q' represents the number of substituents G⁴ on the phenyl ring and is 0, 1, 2, or 3; and G4 moieties are selected from the group consisting of 30 optionally substituted heteroarylalkyl; optionally substituted heteroaryloxy; -S(O)_p(optionally substituted heteroaryl);

- optionally substituted heteroarylalkyloxy;
- \S(O)_p(optionally substituted heteroarylalkyl);
- fused ring-forming bridges attached to and connecting adjacent positions of the phenyl ring, said bridges having the structures:

Sub As

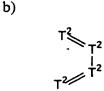
wherein

a)

each Ti independently represents N, CH, or CG4;

T³ represents S, O, CHG⁴, C(H)₂, or NR³; and

binding to the phenyl ring is achieved via terminal atoms T² and T³;



wherein

wherein

each T² independently represents N, CH, or CG⁴;

with the proviso that a maximum of two bridge atoms T^2 may be N; and

binding to the phenyl ring is achieved via terminal atoms T2; and

15

10

c)

$$T^{5}$$
 T^{6}
or
 T^{5}
 T^{6}

20

each T⁵, and T⁶ independently represents O, S, CHG⁴, CH₂, or NR³; and

binding to the phenyl ring is achieved via terminal atoms T⁵; with the provisos that:

- i) a bridge comprising T⁵ and T⁶ atoms may contain a maximum of two heteroatoms O, S, or N; and
- ii) in a bridge comprising T⁵ and T⁶ atoms, when one T⁵ is O, the other T⁵ is S, CHG⁴, CH₂ or NR³;

iii) in a bridge comprising T⁵ and T⁶ atoms, when one T⁵ group and one T⁶ group are O atoms, or two T⁶ groups are O atoms, said O atoms are separated by at least one carbon atom;

أ مان ح

DSB JE T

and with the further provisos that:

- in G¹, G², G³, and G⁴, when two groups R⁶ are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or NR³ to form a N-containing heterocycle of 5 7 ring atoms, and
- when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 2 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio, lower alkanoyloxy, -CO₂R³, -CH₂OR³, -OCO₂R³, -CON(R⁶)₂, -OCO N(R⁶)₂, -NR³CON(R⁶)₂, nitro, and cyano;

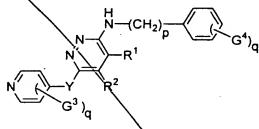
or a pharmaceutically acceptable salt or prodrug thereof.

20

10

15

15. A compound having the generalized structural formula



wherein

 R^1 and R^2 :

i) together form a bridge of structure



wherein binding is achieved via the terminal carbon atoms, and any group G¹ is located on a non-terminal atom of the bridge; or

15

ii) together form a bridge of structure

$$\tau^1$$
 $\tau^1 = \tau^1$

wherein one of the ring members T¹ is N and the others are CH, and binding is achieved via the terminal atoms; and

wherein

m is 0 or an integer 1-2; and

G¹ is a substituent independently selected from the group consisting of

- $-N(R^6)_2$;
- -NR3COR6;
- halogen;
- -OR⁶ wherein R6 represents lower alkyl;
- -NO₂;
- optionally substituted heteroaryloxy;
- optionally substituted heteroarylalkyloxy;

R³ is H or lower alkyl;

20 R⁶ is independently selected from the group consisting of

- H;
- lower alkyl;
- optionally substituted aryl;
- optionally substituted aryl lower alkyl; and

p is 0 or 1;

Y is selected from the group consisting of

- lower alkylene, optionally substituted by OH;
- -CH₂-O-;
 - -S-;

3

-NH-; -S(O)_p-(5-membered heteroaryl)-; -C(CN)(H)-; O-CH₂-; -S(O)-; and -S(Ò)2-; q is 0 or 1; 10 G³ is selected from the group consisting of lower alkyl; -NR3COR6; $-CO_2R^6$; $-CON(R^6)_2$; 15 $-S(O)_2N(R^6)_2$; q' represents the number of substituents G⁴ on the phenyl ring, and is 0, 1, 2, or 3; and G⁴ moieties are selected from the group consisting of 20 optionally substituted heteroarylalkyl; optionally substituted heteroaryloxy; -S(O)_p(optionally substituted heteroaryl); optionally substituted heteroarylalkyloxy; -S(O)_p(optionally substituted heteroarylalkyl); 25 fused ring-forming bridges attached to and connecting adjacent positions of the phenyl ring, said bridges having the structures: a) 30 wherein each T² independently represents N, CH, or CG⁴;

10

15

20

T³ represents S, O, CHG⁴, CH₂, or NR³; and binding to the phenyl ring is achieved via terminal atoms T² and T³;

b) T⁵ T⁶ or T⁵

wherein

each T⁵, and T⁶ independently represents O, S, CHG⁴, CH₂, or NR³; and

binding to the phenyl ring is achieved via terminal atoms T⁵; with the provisos that:

- i) a bridge comprising T⁵ and T⁶ atoms may contain a maximum of two heteroatoms O, S, or N; and
- ii) in a bridge comprising T⁵ and T⁶ atoms, when one T⁵ is O, the other T⁵ is S, CR⁴G⁴, C(R⁴)₂ or NR³;
- iii) in a bridge comprising T⁵ and T⁶ atoms, when one T⁵ group and one T⁶ group are O atoms, or two T⁶ groups are O atoms, said O atoms are separated by at least one carbon atom;

and with the further provisos that:

- in G¹, G², G³, and G⁴, when two groups R⁶ are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or NR³ to form a N-containing heterocycle of 5 6 ring atoms; and
- when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 2 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio, -CO₂R³, -CON(R⁶)₂, nitro, and cyano;
- or a pharmaceutically acceptable salt or prodrug thereof
 - 16. A pharmaceutical composition comprising a compound of claim 13 and a pharmaceutically acceptable carrier.



- 17. A method of treating a mammal having a condition characterized by abnormal angiogenesis or hyperpermiability processes, comprising administering to said mammal an amount of a compound of claim 13 which is effective to treat said condition.
- 18. The method of claim 17, wherein said condition is tumor growth; retinopathy. including diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, and age-related maculal degeneration; rheumatoid arthritis; psoriasis; or a bullous disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis.

19. A compound selected from the group consisting of:

15

a) 4-[4-(4-Chlorophenylamino)phthalazin-1-ylmethyl]pyridin-2-yl carboxylic acid methylamide,

b) 4-[4-(4-Chlorophenylamino)phthalazin-1-ylmethyl]pyridin-2-yl carboxylic acid amide:

20

c) 1-(4-chlorophenylamino)-4-(3-pyridylmethoxy)phthalazine;

methylamide; e) 4-[4-(4-Chlorophenylamino)phthalazin-1-yloxymethyl]pyridin-2-yl carboxylic

d) 4-[4-(4-Chlorophenylamino)phthalazin-1-yloxymethyl]pyridin-2-yl carboxylic acid

acid amide;

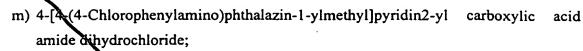
f) 4-[4-(3-Bromophenylamino)phthalazin 1-ylmethyl]-pyridin-2-yl carboxylic acid methylamide;

25

- g) 4-[4-(3-Bromophenylamino)phthalazin-Nylmethyl]-pyridin-2-yl carboxylic acid amide:
- h) 1-(4-chlorophenylamino)-4-[(2-phenyl-4-pyridyl)methyl]phthalazine;
- i) 1-[4-(4-pyridyloxy)phenylamino]-4-(4-pyridylmethyl)phthalazine;
- i) 1-(indan-5-ylamino)-4-(4-pyridylmethyl)phthalazine;

- k) 4-[4-(4-Chlorophenylamino)phthalazin-1-ylmethyl]pyridin-2-yl carboxylic acid methylamide dihydrochloride;
- 1) 4-[4-(4-Chlorophenylamino)phthalazin-1-ylmethyl]pyridin-2-yl carboxylic acid methylamide dimethanesulfonate;





- n) 4-[4-(4-Chlorophenylamino)phthalazin-1-ylmethyl]pyridin-2-yl carboxylic acid amide dimethanesulfonate;
- o) 4-[4-(4-Chlorophenylamino)phthalazin-1-yloxymethyl]pyridin-2-yl carboxylic acid amide dihydrochloride;
- p) 4-[4-(4-Chlorophenylamino)phthalazin-1-yloxymethyl]pyridin-2-yl carboxylic acid amide dimethanesulfonate;
- q) 1-(4-chlorophenylamino)-4-[5-(4-pyridyl)-1H-1,2,4-triazolyl-3-ylthio]phthalazine;
- 10 r) 1-(4-isopropylphenylamino)-4-[5-(4-pyridyl)-1H-1,2,4-triazolyl-3-ylthio]phthalazine
 - s) 1-(4-chlorophenylamino)-4-(4-pyridylsufonyl)phthalazine;
 - t) 1-(4-chlorophenylamino)-4-(4-pyridylsufinyl)phthalaxine;
 - u) 1-(4-chlorophenylamino)-4-(4-pyridylmethoxy)pyridazino
 - v) 1-(indan-5-ylamino)-4-(4-pyridylcyanomethyl)phthalazine; and
 - w) 1-(benzothiazol-6-ylamino)-4-(4-pyridylcyanomethyl)phthalazine.

add A8